Statins: Then and Now

Peter P. Toth, M.D., Ph.D.[a,b]; *Maciej Banach,* M.D., Ph.D.[c]

[a]CGH MEDICAL CENTER, STERLING, ILLINOIS; [b]JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE, BALTIMORE, MARYLAND; [c]MEDICAL UNIVERSITY OF ŁÓDŹ, POLISH MOTHER'S MEMORIAL HOSPITAL RESEARCH INSTITUTE, ŁÓDŹ, POLAND

ABSTRACT: The discovery of statins (3-hydroxy-3-methylglutaryl CoA reductase inhibitors) is a consequence of the highly targeted, arduous search for naturally occurring compounds that inhibit cholesterol biosynthesis. An enormous amount of basic scientific, genetic, and clinical research substantiated the role of lipoprotein-derived cholesterol in atherogenesis. Quantifying the impact of lipid lowering on cardiovascular event rates became an issue of utmost urgency. Although a variety of nonstatin drugs had been tested in clinical trials, they found limited utility in the clinical setting due to lack of mortality reduction or tolerability issues. As multiple prospective randomized statin trials began publishing their results, it became clear that reducing atherogenic lipoprotein burden with these drugs was highly efficacious, safe, and generally well tolerated. Statins have been shown to reduce risk for nonfatal MI, ischemic stroke, need for revascularization, and cardiovascular and all-cause mortality. They have also been shown to stabilize and even regress established atherosclerotic plaque. For the first 2 decades of their use, statin dosing was largely determined by risk-stratified low-density lipoprotein cholesterol (LDL-C) goals. More recently, there has been a transition away from LDL-C goal attainment with a focus more on cardiovascular risk and percent LDL-C reduction. Unfortunately, long-term adherence rates with statin therapy remain low and, even when used, they tend to be underdosed.

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD) remains the leading cause of morbidity and mortality in developed nations, and its incidence continues to rise. Atherogenesis generally begins at an early age and is reversible if intercepted while plaque is not yet fibrotic or calcified. It is now highly established that apoprotein B100-containing lipoproteins, particularly low-density lipoprotein cholesterol (LDL-C), are a primary driver of atherogenesis.[1] The use of lipid-lowering medications to reduce atherogenic lipoprotein burden in serum slows the rate of atherosclerosis disease progression and can even reverse disease if treated aggressively.[2] This manuscript provides a historical perspective on statin development, summarizes major prospective randomized trials that established their efficacy, and reviews some extant issues regarding their use that need further investigation.

SOME HISTORICAL PERSPECTIVE

Investigations performed by Anitschkow in 1913 demonstrated a direct causal relationship between cholesterol and the development of aortic atherosclerotic plaques.[3] In the early 1960s, the Seven Countries Study and Framingham Study both showed a strong association between serum cholesterol levels and risk for myocardial infarction (MI) and death.[4,5] Using preparative ultracentrifugation, Gofman and coworkers demonstrated that elevated levels of low-density lipoprotein cholesterol (LDL-C) were frequently observed in patients who sustained acute cardiovascular (CV) events.[6] Working in Beirut, Lebanon, Khachaturian identified a dose-response relationship between elevations in LDL-C and risk for MI in patients afflicted with the heterozygous and homozygous forms of familial hypercholesterolemia (FH).[7] Goldstein and Brown subsequently elucidated the molecular basis of FH, which they attributed to either reduced hepatocyte cell surface expression of the LDL receptor (LDL-R) or near-complete lack of expression of this receptor in the settings of heterozygous and homozygous FH, respectively.[8,9] Considerable additional clinical and basic scientific investigation supported the conclusion that LDL-C is an important causal agent in atherogenesis.

It was correctly reasoned that if LDL-C plays a critical role in the etiology of atherosclerotic disease, then therapeutic effort should be made to reduce its levels in serum and thus decrease the risk of developing ASCVD. In the World Health Organization Primary Prevention Trial, the fibric acid derivative clofibrate lowered serum total cholesterol (TC) by 9%. Clofibrate treatment significantly reduced the risk for nonfatal MI by 25%, had no effect on fatal MI, but increased all-cause mortality.[10] The Coronary Drug Project, which evaluated the long-term safety and efficacy of five lipid-influencing drugs, demonstrated an increased risk of adverse events with estrogen and thyroid hormone supplementation, a reduced risk of nonfatal MI with nicotinic acid, and no benefit from clofibrate.[11] However, it took 15 years of follow-up to demonstrate a mortality benefit with nicotinic acid, and the resultant dermal flushing made it difficult to tolerate.[12] In the Lipid Research Clinics

Coronary Primary Prevention trial (LRCPPT) that evaluated the efficacy of cholestyramine therapy, a bile acid-binding resin, cholestyramine reduced TC and LDL-C by 13.4% and 20.3%, respectively.[13] After 7.4 years of follow-up, CV mortality and nonfatal MI were significantly reduced by 24% and 19%, respectively; however, all-cause mortality did not differ between the treatment arms. The latter finding coupled with tolerability issues of cholestyramine made for limited adoption of this therapy. However, LRCPPT demonstrated proof of concept; namely, that therapeutic reduction of TC and LDL-C impacts the risk for CV events.

Given the prevalence of dyslipidemia, there was clear urgency in developing new compounds that could substantially reduce the burden of atherogenic lipoprotein in a safe, tolerable, and substantial manner.

DEVELOPMENT OF THE STATINS

Cholesterol is synthesized from acetyl coenzyme A (acetyl CoA) in a 30-step pathway. The rate-limiting step for cholesterol biosynthesis is regulated by 3-hydroxy-3-methylglutaryl CoA reductase (HMG-CoA reductase), which catalyzes the reduction of HMG to mevalonate. Akira Endo hypothesized that some organisms likely produce naturally occurring HMG-CoA reductase inhibitors as a defense mechanism against infection from microbes that require cholesterol or other steroids for their survival.[14] It stood to reason that such molecules might function as a highly effective means of lowering serum cholesterol because they would inhibit its production. The search for a natural HMG-CoA reductase inhibitor required the screening of more than 6,000 microbial species.[15] Mevastatin was isolated from the blue-green mold *Penicillium citrinum*; it had significant structural similarity to HMG-CoA and was a competitive inhibitor of HMG-CoA reductase, with an association constant 10,000-fold higher than HMG-CoA.[16]

In cell culture and in some animal species (i.e., dogs[17] and monkeys[18]), mevastatin proved to be a highly effective inhibitor of cholesterol biosynthesis and reduced serum cholesterol. The stage was set to test the efficacy of mevastatin in a small group of humans. The first patient to receive mevastatin was afflicted with homozygous FH and had a baseline LDL-C of 1,000 mg/dL.[19] Mevastatin reduced her LDL-C by 300 mg/dL, and within 5 months there was evidence that her tendinous xanthomas were regressing. Subsequently, patients with heterozygous FH were treated with mevastatin, and once again LDL-C decreased by approximately 30%.[19] At about this time, investigators at Merck isolated lovastatin from *Aspergillus terreus* and it, too, induced significant reductions in TC and LDL-C.[20] Brown and Goldstein later showed that, in addition to inhibiting HMG-CoA reductase, lovastatin also upregulated LDL-R along the hepatocyte surface via activation of sterol regulatory element binding proteins that increased nuclear expression of LDL-R as intracellular cholesterol levels decreased.[9] Hence, statin therapy also promoted increased clearance of LDL particles as part of their mechanism of action.

Progress was rapid. Multiple other statins were developed, including simvastatin, pravastatin, atorvastatin, fluvastatin, cerivastatin, rosuvastatin, and pitavastatin. Of these, only cerivastatin was found to have an unacceptable adverse event profile and was removed from global markets due to excess risk of rhabdomyolysis, particularly when combined with gemfibrozil.[21]

STATIN OUTCOMES TRIALS

The Scandinavian Simvastatin Survival Study (4S) was the first prospective randomized outcomes trial with a statin, and the results were remarkable.[22] All patients enrolled in 4S had established coronary artery disease (CAD). After 5.4 yrs of follow-up and a 25% decrease in TC and 35% decrease in LDL-C, the following outcomes were significantly reduced: all-cause mortality (30%), risk of a major coronary event (34%), CV mortality (35%), stroke (30%), and coronary interventions (37%). Secondary prevention studies with pravastatin were also positive.[23,24] Primary prevention trials with pravastatin and lovastatin showed a substantial reduction in risk for first-time CV events.[25-27] Atorvastatin therapy was associated with significant reductions in risk for CV events in patients with diabetes mellitus or hypertension.[28,29] The Heart Protection Study demonstrated benefit irrespective of baseline LDL-C.[30] The Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE-IT) and Treating to New Targets (TNT) studies both suggested that when it comes to LDL-C levels, lower is better.[31,32] Among patients with elevated C-reactive protein and an LDL-C < 130 mg/dL, the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) study found that rosuvastatin significantly reduced both CV and all-cause mortality as well as a wide variety of CV end points.[33]

In response to the findings of these and other studies (summarized in Table 1), the National Cholesterol Education Program Adult Treatment Panels recommended risk-stratified LDL-C goals for patients in both the primary and secondary prevention settings.[34,35] Thus, it was recommended that LDL-C be reduced more aggressively as risk for CV events increased, and that the highest-risk patients achieve LDL-C < 70 mg/dL.[36] This approach was replaced in 2014 by a new guideline that

emphasizes statin dose/intensity and percent LDL-C reduction as a function of risk for CV events.[37] Guidelines from around the world continue to emphasize LDL-C reduction to modulate risk for future CV events, and statin therapy continues to be the standard of care for dyslipidemia management. Guidelines agree that all patients with established ASCVD should be on a statin irrespective of baseline TC or LDL-C, although consideration can be given to reducing the dose of a statin if LDL-C falls below 40 mg/dL.

EXTANT ISSUES WITH STATIN THERAPY

Premature Discontinuation

Long-term adherence to statin therapy is poor, even among patients in the secondary prevention setting. Statin discontinuation after 6 months is still in the 50% range,[38,39] a shocking statistic given their risk-to-benefit ratio and the range of CV events they reduce. Unsurprisingly, statin discontinuation is associated with an increase in risk for CV events.[40,41] Negative press associated with statin therapy correlates with risk for statin discontinuation and CV events. It is crucial that patients understand why they are prescribed statins and the implications of premature discontinuation.

Muscle-Related Side Effects

Myalgia is the leading reason for statin discontinuation, and patients frequently stop therapy without informing their physicians. Approaches to managing statin myalgia and improving statin adherence rates have been developed.[42] Statin-related muscle pain is attributable to a highly heterogeneous group of etiologies,[43] and progress in this area has been slow. Patients frequently mistake arthralgias for myalgias. Certainly, the incidence of muscle-related adverse events is higher in clinical practice than what has been observed in clinical trials, largely because patients with a history of myalgia were excluded from participating.[44] We need more objective serum skeletal muscle markers that can help to discriminate true statin intolerance from more nonspecific causes of myalgia.

Serum Transaminase Elevations

It was thought until recently that statins had some degree of hepatic toxicity. The risk of liver failure on a statin is essentially identical to the background rate in the population not treated with statins. There are certainly patients who experience an idiosyncratic rise in serum transaminase levels in response to statins, but this is mainly due to a drug interaction or underlying hepatic steatosis, which can be associated with oscillations in serum transaminase levels secondary to changes in intrahepatic inflammatory tone. The U.S. Food and Drug Administration no longer recommends routine measurement of serum transaminases because of low diagnostic yield.[45]

Reluctance to Titrate Statins

Despite the fact that new guidelines emphasize statin dose and potency, there continues to be reluctance to titrate statins out of safety concerns.[46] Side-effect profiles are slightly impacted as statin dosages are increased. However, the benefits far outweigh the risks. There also continues to be lingering fear that we are driving LDL-C levels "too low." LDL particles are an end product of lipoprotein metabolism and, to a large degree, represent spent, garbage lipid. There is really not much one does with LDL particles. However, they are clearly toxic to arterial walls. Genome-wide association studies and Mendelian inheritance studies uniformly agree that any genetic polymorphism that confers a lower LDL-C is atheroprotective, and the opposite is also true: Any polymorphism that increases LDL-C also increases risk for ASCVD.[47] Based on recent randomized studies, not only is it true that "lower is better" but "lowest is best." In both the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)[48] and Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) trials,[49] the subgroups with the lowest attained LDL-C had the lowest event rates, with no increased risk for adverse events.

Cognitive Function

There are bloggers and talk show guests insisting that statins cause cognitive impairment. To date, no such relationship has been identified.[50,51] Neither the Heart Protection Study[52] nor the Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER) trial,[53] which used validated cognitive batteries in older patients, were able to detect a statin-induced reduction in cognitive capacity. More recently, the Evaluating PCSK9 Binding Antibody Influence on Cognitive Health in High Cardiovascular Risk Subjects (EBBINGHAUS) study and the Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab (ODYSSEY Outcomes) study failed to demonstrate any adverse effect on cognition when combining either evolocumab or alirocumab and statin therapy, even at very low levels of attained LDL-C.[54,55] However, some patients insist that they experience memory impairment or cognitive dysfunction that resolve with statin discontinuation. Consistent with guideline recommendations, if a patient experiences cognitive impairment on a statin, it is important to rule out other biochemical or anatomical etiologies before simply stopping the statin, especially in high-risk patients. Clinicians may also consider switching to a different statin.

STUDY	DRUG	DESIGN	OUTCOMES
Primary prevention studies			
AFCAPS/TexCAPS	Lovastatin, 20-40 mg/d vs placebo	6,605 men and women	40% reduction in fatal and nonfatal MI; 37% reduction in first ACS; 33% reduction in coronary revascularizations; 32% reduction in unstable angina
ASCOT	Atorvastatin 10 mg/d vs placebo	10,305 hypertensive men (n = 8,463) and women (n = 1,942) with treated high BP and no previous CAD	36% reduction in total CHD/nonfatal MI; 27% reduction in fatal and nonfatal stroke; total coronary event reduced by 29%; fatal and nonfatal stroke reduced by 27%
CARDS	Atorvastatin 10 mg/d vs placebo	2,838 patients with type 2 diabetes mellitus and 1 CHD risk factor	37% reduction in major cardiovascular events; 27% reduction in total mortality; 13.4% reduction in acute CVD events; 36% reduction in acute coronary events; 48% reduction in stroke
Heart Protection Study	Simvastatin 40 mg/d vs placebo	20,536 high-risk patients (previous CHD, other vascular disease, hypertension among men aged > 65 y, or diabetes)	25% reduction in all-cause and coronary death rates and in strokes; need for revascularization reduced by 24%; fatal and nonfatal stroke reduced by 25%; nonfatal MI reduced by 38%; coronary mortality reduced by 18%; all-cause mortality reduced by 13%; cardiovascular event rate reduced by 24%
PROSPER	Pravastatin 40 mg/d vs placebo	5,804 men (n = 2,804) and women (n = 3,000) aged 70-82 y	15% reduction in combined end point (fatal/nonfatal MI or stroke); 19% reduction in total/nonfatal CHD; no effect on stroke (but 25% reduction in TIA)
WOSCOPS[6]	Pravachol therapy 40 mg/d vs placebo	6,595 men	CHD death in nonfatal MI reduced by 31%; CVD death reduced by 32%; total mortality reduced by 22%
JUPITER	Rosuvastatin 20 mg/d vs placebo	17,802 men (> 50 y) and women (> 60 y) with no history of CAD or DM, entry LDL < 130 mg/dL, and CRP > 2.0 mg/L	44% reduction in primary end point in major coronary events; 65% reduction in nonfatal MI; 48% reduction in nonfatal stroke; 46% reduction in need for revascularization; 20% reduction in all-cause mortality

Table 1. Continued on next page.

Prospective randomized statin trials in both primary and secondary prevention. Reprinted with permission.

STUDY	DRUG	DESIGN	OUTCOMES
Secondary prevention studies			
4S	Simvastatin 20 mg/d vs placebo	4,444 patients with angina pectoris or history of MI	Coronary mortality reduced by 42%; myocardial revascularization reduced by 37%; all-cause mortality reduced by 30%; nonfatal major coronary event reduced by 34%; fatal and nonfatal stroke reduced by 30%
AVERT	Atorvastatin 80 mg/d vs angioplasty and usual care	341 patients with stable CAD	36% reduction in ischemic event; delayed time to first ischemic event reduced by 36%
CARE	Pravastatin 40 mg/d vs placebo	3,583 men and 576 women with history of MI	Death from CHD or nonfatal MI reduced by 24%; death from CHD reduced by 20%; nonfatal MI reduced by 23%; fatal MI reduced by 37%; CABG or PTCA reduced by 27%
IDEAL	Atorvastatin 80 mg/d vs simvastatin 20-40 mg/day	8,888 men and women with CHD	Major cardiac events reduced by 13%, nonfatal MI reduced by 17%, revascularization reduced by 23%, peripheral arterial disease reduced by 24%
LIPID	Pravachol 40 mg/d vs placebo	9,014 patients	Coronary mortality reduced by 24%; stroke reduced by 19%; fatal CHD or nonfatal MI reduced by 24%; fatal or nonfatal MI reduced by 29%
LIPS	Fluvastatin 40 mg/d vs placebo	1,667 men and women aged 18-80 y post-angioplasty for CAD	22% lower rate in major coronary events (e.g., cardiac deaths, nonfatal MI, or reintervention procedure)
MIRACL	Atorvastatin 80 mg/d vs placebo	3,086 patients with ACS	Reduction in composite end point by 16%; ischemia reduced by 26%; stroke reduced by 50%
PROVE IT	Atorvastatin 80 mg/d vs pravastatin 40 mg/day	4,162 patient with ACS	16% reduction in composite end point; 14% reduction in CHD death, MI, or revascularization; revascularizations reduced by 14%; unstable angina reduced by 29%
REVERSAL	Atorvastatin 80 mg/d vs pravastatin 40 mg/day	654 patients with CAD	Atheroma: atorvastatin 0.4%, pravastatin 2.7%, difference of -3.1%, $P = .02$
TNT	Atorvastatin 10 mg/d vs 80 mg/day	10,003 patients with CHD and LDL cholesterol 130-250 mg/dL	22% reduction in composite end point; MI reduced by 22%; stroke reduced by 25%

Abbreviations: ACS: acute coronary syndrome; CABG: coronary artery bypass grafting; CAD: coronary artery disease; CHD: coronary heart disease; LDL: low-density lipoprotein; MI: myocardial infarction; PTCA: percutaneous transluminal coronary angioplasty. Trial acronyms: AFCAPS/TexCAPS: The Air Force/Texas Coronary Atherosclerosis Prevention Study: Implications for Preventive Cardiology in the General Adult US Population; ASCOT: Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm; CARDS: Collaborative Atorvastatin Diabetes Study; PROSPER: Pravastatin in elderly individuals at risk of vascular disease; WOSCOPS: West of Scotland Coronary Prevention Study; 4S: The Scandinavian Simvastatin Survival Study; AVERT: Atorvastatin versus Revascularization Treatment Investigators; CARE: Cholesterol and Recurrent Events Trial; IDEAL: Incremental Decrease in End Points Through Aggressive Lipid Lowering Study; JUPITER: The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; LIPID: Long-Term Intervention with Pravastatin in Ischemic Disease; LIPS: Lescol Intervention Prevention Study; MIRACL: Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering Study; PROVE IT: Pravastatin or Atorvastatin Evaluation and Infection Therapy Study; REVERSAL: The REVERSing Atherosclerosis with Aggressive Lipid Lowering Study; TNT: Treating to New Targets Trial

Table 1. Continued

Statins and Diabetes Mellitus

The JUPITER trial investigators reported an increase in risk for diabetes mellitus (DM) with rosuvastatin therapy. However, rosuvastatin accelerated time to new-onset DM compared to placebo by an average of only 5.4 weeks.[56] A subsequent meta-analysis suggested that 1,000 patients have to be treated annually with low-dose statin therapy to induce one new case of DM; with moderate- to high-dose statin therapy, one person will develop DM for every 500 treated per year.[57] Hence, the risk is relatively low. Moreover, it has been shown that the patients who develop DM on statin therapy are already prediabetic: The greater their number of risk factors for metabolic syndrome, the higher their risk for DM.[58] This must be actively contextualized for patients. Moreover, it should also be made clear that diabetic patients derive as much benefit from statin therapy as do nondiabetics.

C-Reactive Protein

Atherosclerosis is an inflammatory disease. High-sensitivity C-reactive protein (hs-CRP) levels in serum correlate with risk for cardiovascular events. The Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) demonstrated that the antagonism of interleukin-1B with a monoclonal antibody reduced both hs-CRP and risk for CV events independent of changes in lipoprotein cholesterol levels.[59] Post hoc analyses of multiple statin trials have shown that the dual targets of LDL-C < 70 mg/dL and CRP < 1.0 provide the highest levels of risk reduction.[60,61] It is time to assess whether or not hs-CRP should be a target of statin therapy.

Conflict of Interest Disclosure:
Dr. Toth conducts research on behalf of Amarin, Amgen, and Kowa and is a consultant for Amarin, Amgen, Kowa, Merck, Novo-Nordisk, Theravance, Regeneron, and Sanofi. Dr. Banach is a consultant for Abbott/Mylan, Abbott Vascular, Actavis, Akcea, Amgen, Biofarm, Daiichi Sankyo, Esperion, Krka Pharma, Eli Lilly, MSD, Resverlogix, Sanofi-Aventis, and Valeant and conducts research on behalf of Sanofi and Valeant.

Keywords:
3-hydroxy-3-methylglutaryl-coenzyme A reductase, atherosclerosis, cardiovascular events, low-density lipoprotein cholesterol, lovastatin, mevastatin

KEY POINTS

- Statins represent a vital therapy for patients with dyslipidemia and for attenuating cardiovascular (CV) risk in both primary and secondary prevention.
- The discovery of statins was not happenstance; it was the product of targeted investigation to find naturally occurring compounds that inhibit the rate-limiting step of cholesterol biosynthesis.
- Dyslipidemia and atherosclerotic CV disease are widely prevalent throughout the world. Despite the fact that statins reduce CV events and mortality, these agents are underutilized and frequently underdosed.
- Statins have been shown to be safe and efficacious over 4 decades of intensive investigation. The role of low-density lipoprotein cholesterol (LDL-C) in atherogenesis is among the most intensively studied issues in all of medicine.
- Patients need to be actively educated about the risks of statin therapy, but these risks should be very carefully contextualized. For instance, risk of new-onset diabetes is low, and we no longer believe there is a threshold of LDL-C below which risk for adverse events increases.
- Statin discontinuation rates remain unacceptably high. This is an urgent issue that must be addressed at both an individual patient and societal level.

REFERENCES

1. Steinberg D, Gotto AM Jr. Preventing coronary artery disease by lowering cholesterol levels: fifty years from bench to bedside. JAMA. 1999 Dec 1;282(21):2043-50.
2. Nissen SE, Nicholls SJ, Sipahi I, et al.; ASTEROID Investigators. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA. 2006 Apr 5;295(13):1556-65.
3. Anitschkow N. Über die Veränderungen der Kaninchenaorta bei experimenteller Cholesterinsteatose. Beitr Pathol Anat. 1913;56:379-404.
4. Keys A, Aravanis C, Blackburn HW, et al. Epidemiological studies related to coronary heart disease: characteristics of men aged 40-59 in seven countries. Acta Med Scand Suppl. 1966;460:1-392.
5. Kannel WB, Dawber TR, Kagan A, Revotskie N, Stokes J 3rd. Factors of risk in the development of coronary heart disease–six year follow-up experience. The Framingham Study. Ann Intern Med. 1961 Jul;55:33-50.
6. Gofman JW, Lindgren F. The role of lipids and lipoproteins in atherosclerosis. Science. 1950 Feb 17;111(2877):166-71.
7. Khachadurian AK. The Inheritance of Essential Familial Hypercholesterolemia. Am J Med. 1964 Sep;37:402-7.
8. Goldstein JL, Brown MS. Familial hypercholesterolemia: identification of a defect in the regulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase activity associated with overproduction of cholesterol. Proc Natl Acad Sci U S A. 1973 Oct;70(10):2804-8.

9. Goldstein JL, Brown MS. The LDL receptor. Arterioscler Thromb Vasc Biol. 2009 Apr;29(4):431-8.

10. W.H.O. cooperative trial on primary prevention of ischaemic heart disease using clofibrate to lower serum cholesterol: mortality follow-up. Report of the Committee of Principal Investigators. Lancet. 1980 Aug 23;2(8191):379-85.

11. Clofibrate and niacin in coronary heart disease. JAMA. 1975 Jan 27;231(4):360-81.

12. Canner PL, Berge KG, Wenger NK, et al. Fifteen year mortality in Coronary Drug Project patients: long-term benefit with niacin. J Am Coll Cardiol. 1986 Dec;8(6):1245-55.

13. The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. JAMA. 1984 Jan 20;251(3):351-64.

14. Endo A. The discovery and development of HMG-CoA reductase inhibitors. J Lipid Res. 1992 Nov;33(11):1569-82.

15. Endo A. A gift from nature: the birth of the statins. Nat Med. 2008 Oct;14(10):1050-2.

16. Endo A. A historical perspective on the discovery of statins. Proc Jpn Acad Ser B Phys Biol Sci. 2010;86(5):484-93.

17. Tsujita Y, Kuroda M, Tanzawa K, Kitano N, Endo A. Hypolipidemic effects in dogs of ML-236B, a competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase. Atherosclerosis. 1979 Mar;32(3):307-13.

18. Kuroda M, Tsujita Y, Tanzawa K, Endo A. Hypolipidemic effects in monkeys of ML-236B, a competitive inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A reductase. Lipids. 1979 Jun;14(6):585-9.

19. Yamamoto A, Sudo H, Endo A. Therapeutic effects of ML-236B in primary hypercholesterolemia. Atherosclerosis. 1980 Mar;35(3):259-66.

20. Alberts AW, Chen J, Kuron G, et al. Mevinolin: a highly potent competitive inhibitor of hydroxymethylglutaryl-coenzyme A reductase and a cholesterol-lowering agent. Proc Natl Acad Sci U S A. 1980 Jul;77(7):3957-61.

21. Furberg CD, Pitt B. Withdrawal of cerivastatin from the world market. Curr Control Trials Cardiovasc Med. 2001;2(5):205-7.

22. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet. 1994 Nov 19;344(8934):1383-9.

23. Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. N Engl J Med. 1998 Nov 5;339(19):1349-57.

24. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. N Engl J Med. 1996 Oct 3;335(14):1001-9.

25. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. N Engl J Med. 1995 Nov 16;333(20):1301-7.

26. Shepherd J, Blauw GJ, Murphy MB, et al.; PROSPER study group. PROspective Study of Pravastatin in the Elderly at Risk. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet. 2002 Nov 23;360(9346):1623-30.

27. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS. Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA. 1998 May 27;279(20):1615-22.

28. Colhoun HM, Betteridge DJ, Durrington PN, et al.; CARDS investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet. 2004 Aug 21-27;364(9435):685-96.

29. Sever PS, Dahlöf B, Poulter NR, et al.; ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet. 2003 Apr 5;361(9364):1149-58.

30. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20, 536 high-risk individuals: a randomised placebo-controlled trial. Lancet. 2002 Jul 6;360(9326):7-22.

31. Cannon CP, Braunwald E, McCabe CH, et al.; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med. 2004 Apr 8;350(15):1495-504.

32. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med. 2005 Apr 7;352(14):1425-35.

33. Ridker PM, Danielson E, Fonseca FA, et al.; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med. 2008 Nov 20;359(21):2195-207.

34. Summary of the second report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). JAMA. 1993 Jun 16;269(23):3015-23.

35. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA. 2001 May 16;285(19):2486-97.

36. Grundy SM, Cleeman JI, Merz CN, et al.; National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation. 2004 Jul 13;110(2):227-39.

37. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Jun 24;129(25 Suppl 2):S1-45.

38. Zhang H, Plutzky J, Skentzos S, et al. Discontinuation of statins in routine care settings: a cohort study. Ann Intern Med. 2013 Apr 2;158(7):526-34.

39. Lin I, Sung J, Sanchez RJ, et al. Patterns of Statin Use in a Real-World Population of Patients at High Cardiovascular Risk. J Manag Care Spec Pharm. 2016 Jun;22(6):685-98.

40. Daskalopoulou SS, Delaney JA, Filion KB, Brophy JM, Mayo NE, Suissa S. Discontinuation of statin therapy following an acute myocardial infarction: a population-based study. Eur Heart J. 2008 Sep;29(17):2083-91.

41. Nielsen SF, Nordestgaard BG. Negative statin-related news stories decrease statin persistence and increase myocardial infarction and cardiovascular mortality: a nationwide prospective cohort study. Eur Heart J. 2016 Mar 14;37(11):908-16.

42. Banach M, Rizzo M, Toth PP, et al. Statin intolerance - an attempt at a unified definition. Position paper from an International Lipid Expert Panel. Expert Opin Drug Saf. 2015 Jun;14(6):935-55.

43. Toth PP, Patti AM, Giglio RV, et al. Management of Statin Intolerance in 2018: Still More Questions Than Answers. Am J Cardiovasc Drugs. 2018 Jun;18(3):157-73.

44. Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients–the PRIMO study. Cardiovasc Drugs Ther. 2005 Dec;19(6):403-14.

45. U.S. Food and Drug Administration [Internet]. Silver Spring, MD: U.S. Food and Drug Administration; c2018. FDA Drug Safety Communication: Important safety label changes to cholesterol-lowering statin drugs; 2016 Jan 19 [cited 2018 Oct 2]. Available from https://www.fda.gov/Drugs/DrugSafety/ucm293101.htm.

46. Power TP, Ke X, Zhao Z, et al. Clinical characteristics, patterns of lipid-lowering medication use, and health care resource utilization and costs among patients with atherosclerotic cardiovascular disease. Vasc Health Risk Manag. 2018 Feb 5;14:23-36.

47. Ference BA, Yoo W, Alesh I, et al. Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. J Am Coll Cardiol. 2012 Dec 25;60(25):2631-9.

48. Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med. 2015 Jun 18;372(25):2387-97.

49. Sabatine MS, Giugliano RP, Keech AC, et al.; FOURIER Steering Committee and Investigators. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med. 2017 May 4;376(18):1713-22.

50. Gauthier JM, Massicotte A. Statins and their effect on cognition: Let's clear up the confusion. Can Pharm J (Ott). 2015 May;148(3):150-5.

51. Rojas-Fernandez CH, Goldstein LB, Levey AI, Taylor BA, Bittner V.; The National Lipid Association's Safety Task Force. An assessment by the Statin Cognitive Safety Task Force: 2014 update. J Clin Lipidol. 2014 May-Jun;8(3 Suppl):S5-16.

52. Collins R, Armitage J, Parish S, Sleight P, Peto R; Heart Protection Study Collaborative Group. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. Lancet. 2004 Mar 6;363(9411):757-67.

53. Trompet S, van Vliet P, de Craen AJ, et al. Pravastatin and cognitive function in the elderly. Results of the PROSPER study. J Neurol. 2010 Jan;257(1):85-90.

54. Giugliano RP, Mach F, Zavitz K, et al. Cognitive Function in a Randomized Trial of Evolocumab. N Engl J Med. 2017 Aug 17;377(7):633-43.

55. Schwartz GG, Steg PG, Szarek M, et al.; ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and Cardiovascular Outcomes after Acute Coronary Syndrome. N Engl J Med. 2018 Nov 29;379(22):2097-2107.

56. Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. Lancet. 2012 Aug 11;380(9841):565-71.

57. Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA. 2011 Jun 22;305(24):2556-64.

58. Waters DD, Ho JE, DeMicco DA, et al. Predictors of new-onset diabetes in patients treated with atorvastatin: results from 3 large randomized clinical trials. J Am Coll Cardiol. 2011 Apr 5;57(14):1535-45.

59. Ridker PM, Everett BM, Thuren T, et al.; CANTOS Trial Group. Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease. N Engl J Med. 2017 Sep 21;377(12):1119-31.

60. Bohula EA, Giugliano RP, Cannon CP, et al. Achievement of dual low-density lipoprotein cholesterol and high-sensitivity C-reactive protein targets more frequent with the addition of ezetimibe to simvastatin and associated with better outcomes in IMPROVE-IT. Circulation. 2015 Sep 29;132(13):1224-33.

61. Ridker PM, Danielson E, Fonseca FA, et al. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. Lancet. 2009 Apr 4;373(9670):1175-82.